REMARKS

In the Office Action on page 2, claims 8, 9 and 14 were rejected under 35 U.S.C. §112, first paragraph.

Reconsideration is requested.

The Examiner arguments on pages 2-10 of the Office Action have been considered and it is believed that the applicant's current amendments render these arguments moot. Specifically, Applicant has rewritten Claims 8-9 and 14 in accordance with the Examiner's suggestion of allowable subject matter. The grounds for rejection in these claims have now been removed and it is requested that the §112, first paragraph rejections be withdrawn.

In the Office Action on page 10, claims 1, 3, 5-9 and 11-18 were rejected under 35 U.S.C. §112, second paragraph.

Reconsideration is requested.

Claim 1 has been amended to avoid each formal objection that was raised by the Examiner. Specifically, the number of parentheses has been corrected in accordance with claim 1 as originally filed. Also, the period four lines from the end of Claim 1 has been removed.

Claim 3 has been amended to make it dependent on claim 1 instead of claim 2. Also, the term "chinyl" has been defined as "quinyl" and corresponds to the group 1,3,4,5-tetrahydroxycyclohaxancarboxyl (see the Merck Index under Quinic Acid or CAS REF NUM 77-95-2 (the corresponding acid)). An amendment has been made to Claim 3 to replace "chinyl" with "quinyl". The spelling of glycopiranos-1-yl has been amended in "at", "an", "ap" and "au". Also the period following the name of compound "am" has been eliminated.

In Claim 5 the term "general" has been removed.

The grounds for rejection in these claims have now been removed and it is requested that the §112, second paragraph rejections be withdrawn.

In the Office Action on page 11, claim 1 was rejected under 35 U.S.C. §102(b) as being anticipated by Kyoko JP 06172385.

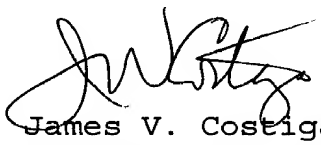
Reconsideration is requested.

The last 2 lines of Claim 1 have been amended to include a disclaimer reading "wherein when $R_1=R_2=$ a side chain of trytophan and $R_4= CH_2OH$ then R_3 is not isopropyl". It is believed that this disclaimer removes the grounds for rejection based on Kyoko JP 06172385. It is therefore requested that the §102 (b) rejection be withdrawn.

Based on the amendments, applicant respectfully submits that all of Claims 1, 3, 5-9 and 11-18 are now allowable over the prior art and that the present application is in proper form for allowance.

Favorable consideration and early allowance is respectfully requested and earnestly solicited.

Respectfully submitted,



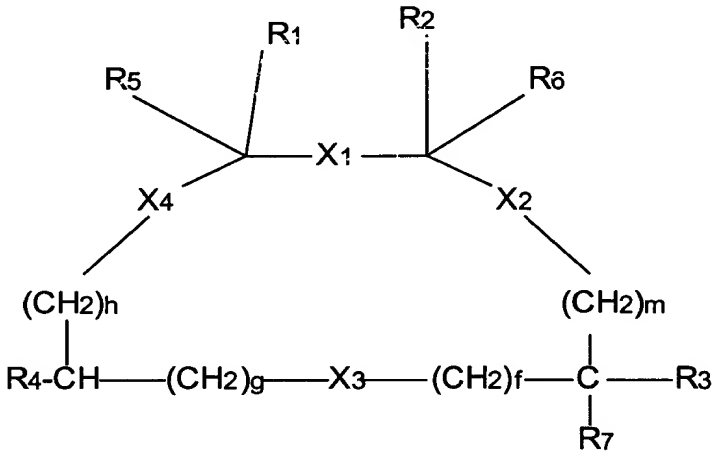
James V. Costigan
Registration No. 25,669

MAILING ADDRESS

Hedman & Costigan, P.C.
1185 Avenue of the Americas
New York, N.Y. 10036
(212) 302-8989

MARKED UP COPY OF AMENDMENTS TO CLAIMS

1. (Amended three times) A monocyclic compound having the formula (1):



in which:

X_1, X_2, X_3, X_4, which may be the same or different from one another, is selected from the group consisting of -CONR-, -NRCO-, -OCO-, -COO-, $-CH_2NR-$ and $-NR-CH_2-$, where R is H or a C_{1-3} alkyl or benzyl;

f, g, h, m, which may be the same or different from one another, may be 0 or 1;

R_1 and R_2 which may be the same or different from one another, represent theside chain of a natural amino acid selected from the group consisting of tryptophan, phenylalanine, tyrosine and histidine, or the side chain of a non-natural amino acid selected from the group consisting of:

tryptophan and phenylalanine, either mono- or di-substituted with residues selected from the group

consisting of C_{1-3} alkyl or halo-alkyl, C_{1-3} alkoxyl or amino-alkoxyl, halogen, OH, NH_2 and $NR_{13}R_{14}$, where R_{13} and R_{14}, which may be the same or different from one another, represent a hydrogen or C_{1-3} alkyl group;

R_3 is selected from the group consisting of:

- linear or branched alkyl having the formula C_nH_{2n+1} with n=1-5 (selected from the group consisting of methyl, ethyl, propyl, isopropyl, n-butyl and t-butyl) cycloalkyl or alkylcycloalkyl of formula C_nH_{2n-1} with n=5-9 (selected from the group consisting of: cyclopentyl, cyclohexyl and methylcyclohexyl)

$-(CH_2)_r-Ar_1$, where r=1 or 2 and where Ar_1 is an aromatic group selected from the group consisting of: α-naphthyl, β-naphthyl, phenyl, indole, said Ar_1 group being possibly substituted with a maximum of two residues selected from the group consisting of: C_{1-3} alkyl, CF_3, C_{1-3} alkoxyl, Cl, F, OH and NH_2;

R_4 represents an L-Q group where:

L is a chemical bond of CH_2, and

Q is selected from the group consisting of:

- OH, NH_2, NR_9R_{10}, OR_{11}, and where R_9 and R_{10}, which may be the same or different from one another, represent a hydrogen or C_{1-3}alkyl group, C_{1-3}hydroxy alkyl, C_{1-3}dihydroxyaklyl, C_{1-3}alkyl-$CONHR_{12}$ (wherein R_{12} is a monoglycosidic group derived from D or L pentoses or hexoses (selected from the group consisting of ribose, arabinose, glucose, galactose, fructose, glucosamine, galactosamine N-acetylglucosamine and N-acetylgalactosamine)), C_{1-3}alkyltetrazole, C_{1-3}alkyl-COOH or wherein R_9R_{10} are joined together to form with the N atom a morpholine or a piperidine ring and where R_{11} is a C_{1-3} alkyl chain, or a C_{2-4} amino-alkyl chain;

$NHCOR_8$ wherein R_8 is a cyclohexane containing from 2 to 4 OH groups, C_{1-6} alkyl chain containing a polar group (chosen in the group consisting of NH_2, COOH, $CONHR_{12}$, (wherein R_{12} is as hereabove defined) or [()[1,4']bipiperidine)]

- COOH, $COOR_{17}$ or $CONHR_{12}$, wherein R_{12} is as hereabove defined and R_{17} is as R_{12} or a group 4-nitrobenzyl[.]

- R_5, R_6, R_7 are H_2 in which the carbon atom that carries the substituents R_3 and R_7 has configuration R;

wherein when R_1=R_2= a side chain of trytophan and R_4= CH_2OH then R_3 is not isopropyl.

3. (amended three times) A compound according to Claim [2] 1 selected from:

(a) Cyclo{-Suc-Trp-Phe-[(R)-NH-CH($CH_2C_6H_5$)-CH_2-NH]}

(b) Cyclo{-Suc-Trp-Phe-[(S)-NH-CH($CH_2C_6H_5$)-CH_2-NH]}

(c) Cyclo{-Suc-Trp-Phe-[(R)-NH-CH($CH_2C_6H_{11}$)-CH_2-NH]}

(d) Cyclo{-Suc-Trp-Phe-[(R)-NH-CH($CH_2C_6H_4$(4-OCH_3))-CH_2-NH]}

(e) Cyclo{-Suc-Trp(5F)-Phe-[(R)- NH-CH($CH_2C_6H_5$)-CH_2-NH]}

(f) Cyclo{-Suc-Trp(Me)-Phe-[(R)- NH-CH($CH_2C_6H_5$)-CH_2-NH]}

(g) Cyclo{-Suc-Phe(3,4-Cl)-Phe-[(R)- NH-CH($CH_2C_6H_5$)-CH_2-NH]}

(h) Cyclo{-Suc-Trp-Phe(3,4-Cl)-[(R)- NH-CH($CH_2C_6H_5$)-CH_2-NH]}

(i) Cyclo{-Suc-Trp-Tyr-[(R)-NH-CH($CH_2C_6H_5$)-CH_2-NH]}

(j) Cyclo{-Suc-Trp-Phe-[(R)-NH-CH($CH_2C_6H_3$-3,4-diCl)-CH_2-NH]}

(k) Cyclo{-Suc-Trp-Phe-[(R)-NH-CH($CH_2C_6H_4$-4-OH)-CH_2-NH]}

(l) Cyclo{-Suc-Trp-Phe-[(R)-NH-CH(CH_2-CH_2-C_6H_5)-CH_2-NH]}

(m) Cyclo{-Suc-Trp-Phe-[(R)-NH-CH(CH_2-2-napthyl)-CH_2-NH]}

(n) Cyclo{-Suc-Trp-Phe-[(R)-NH-CH(CH_2-indol-3-yl)-CH_2-NH]}

(o) Cyclo{-Suc-Trp-Phe-[(R)-NH-CH(CH_2-5-F-indol-3-yl)-CH_2-NH]}

(p) Cyclo{-Suc-Trp-Phe-[(R)-NH-CH(CH_2-C_6H_4-3-F)-CH_2-NH]}

(q) Cyclo{-Suc-Trp-Phe-[(R)-NH-CH(CH_2-C_6H_3-3,4-diF-CH_2-NH]-}

(r) Cyclo{-Suc-Trp-Phe-[(R)-NH-CH(CH_2-C_6H_4-4-CF_3-CH_2-NH]-}

(s) Cyclo{-Suc-Trp-Phe-[(R)-NH-CH_2-CH($CH_2C_6H_5$)-NH]}

(t) Cyclo{-Suc-Trp-Phe-[(S)-NH- CH_2-CH($CH_2C_6H_5$)-NH]}

(u) Cyclo{-Trp-Phe-[(R)-NH-CH(CH_2-C_6H_5)-CH_2-NH]-$(CH_2)_3CO$-}

(v) Cyclo{-Trp-Phe-[(R)-NH-CH(CH_2-C_6H_5)-CH_2-N(CH_3)]-$(CH_2)_3CO$-}

(w) Cyclo{-Suc[1(S)-NH_2]-Trp-Phe-[(R)NH-CH(CH_2-C_6H_5)-CH_2NH]-}

(x) Cyclo{-Suc[1(R)-NH_2]-Trp-Phe-[(R)NH-CH(CH_2-C_6H_5)-CH_2NH]-}

(y) Cyclo{-Suc[2(S)-NH_2]-Trp-Phe-[(R)NH-CH(CH_2-C_6H_5)-CH_2NH]-}

(z) Cyclo{-Suc[2(R)-NH_2]-Trp-Phe-[(R)NH-CH(CH_2-C_6H_5)-CH_2NH]-}

(aa) Cyclo{-Suc[1(S)-NH(CH_3)]-Trp-Phe-[(R)NH-CH(CH_2-C_6H_5)-CH_2NH]-}

(ab) Cyclo{-Suc[1-COO(CH_2-C_6H_4-4-NO_2)]-Trp-Phe-[(R)NH-CH(CH_2-C_6H_5)-CH_2NH]-}

(ac) Cyclo{-Suc(1-COOH)-Trp-Phe-[(R)-NH-CH(CH_2-C_6H_5)-CH_2-NH]}

[Cyclo{-Suc(1-COOH)-Trp-Phe-[(R)-NH-CH(CH_2-C_6H_5)-CH_2-NH]}]

(ad) Cyclo{-Suc(1-OH)-Trp-Phe-[(R)-NH-CH(CH_2-C_6H_5)-CH_2-NH]}

(ae) Cyclo{-Suc(2-COOH)-Trp-Phe-[(R)-NH-CH(CH_2-C_6H_5)-CH_2-NH]}

(af) Cyclo{-Suc(2-OH)-Trp-Phe-[(R)-NH-CH(CH_2-C_6H_5)-CH_2-NH]}

(ag) Cyclo{-Suc[1(S)-(2H-tetrazolyl-5-ylmethyl)amino]-Trp-Phe-[(R)-NH-CH(CH_2-C_6H_5)-CH_2-NH]-} trifluoro[-]acetic acid

(ah) Cyclo{-Suc[1(S)-(morpholin-4-yl)]-Trp-Phe-[(R)-NH-CH(CH_2-C_6H_5)-CH_2-NH]-} trifluoroacetic acid

(ai) Cyclo{-Suc[1(S)-N(CH_3)$_2$]-Trp-Phe-[(R)-NH-CH(CH_2-C_6H_5)-CH_2-NH]-} trifluoroacetic acid

(aj) Cyclo{-Suc[1(S)-(piperidin-4-yl]-Trp-Phe-[(R)-NH-$CH(CH_2-C_6H_5)-CH_2-NH]$-} trifluoroacetic acid

(ak) Cyclo{-Suc[1(S)-$(N(CH_2CH_2OH)_2)$]-Trp-Phe-[(R)-NH-$CH(CH_2-C_6H_5)-CH_2-NH$]} trifluoroacetic acid

(al) Cyclo{-Suc[1(S)-$(N(CH_2CH(OH)CH_2OH)$]-Trp-Phe-[(R)-NH-$CH(CH_2-C_6H_5)-CH_2-NH$]-} trifluoroacetic acid

(am) Cyclo{-Suc[1(S)-(3-carboxypropanoyl)amino]-Trp-Phe-[(R)-NH-$CH(CH_2-C_6H_5)-CH_2-NH$]-}[.]

(an) Cyclo{-Suc[1(S)-[3-N'-ß-D-glucop[i]yranos-1-yl)-carboxamidopropanoyl]amino]-Trp-Phe-[(R)NH-$CH(CH_2-C_6H_5)-CH_2NH$]-}

(ao) Cyclo{-Suc[1(S)-[(carboxymethyl)amino]-Trp-Phe-[(R)-NH-$CH(CH_2-C_6H_5)-CH_2-NH$]-} trifluoroacetic acid

(ap) Cyclo{-Suc[1(S)-[N'-ß-D-glucop[i]yranos-1-yl)-carboxyamideomethyl]amino]-Trp-Phe-[(R)-NH-$CH(CH_2-C_6H_5)-CH_2-NH$]-} trifluoroacetic acid

(aq) Cyclo{-Suc[1(S)-([chinyl]quinyl)amine]-Trp-Phe-[(R)-NH-$CH(CH_2-C_6H_5)-CH_2-NH$]-}

(ar) Cyclo{-Suc[1(S)-(4-aminobutanoyl)amino]-Trp-Phe-[(R)-NH-$CH(CH_2-C_6H_5)-CH_2-$ NH]-} trifluoroacetic acid

(as) Cyclo{-Suc[1(S)-[1,4')bipiperidin-1-yl]acetamido]-Trp-Phe-[(R)-NH-$CH(CH_2-C_6H_5)-CH_2-NH$]-} trifluoroacetic acid

(at) Cyclo{-Suc[1-N-(ß-D-glucop[i]yranos-1-yl)-carboxyamido]-Trp-Phe-[(R)-NH-$CH(CH_2-C_6H_5)-CH_2-NH$]-}

(au) Cyclo{-Suc[1(S)-[N'-(2-N-acetyl-ß-D-glucop[i]yranos-1-yl)-carboxyamido]-Trp-Phe-[(R)-NH-$CH(CH_2-C_6H_5)-CH_2-NH$]-}.

5. (Amended three times) A composition comprising a compound of [general] formula (I) according to Claim 1 in combination with a suitable carrier or excipient.

8. (twice amended) [A composition according to Claim 7, adapted for use in the treatment of] A method of inhibiting

bronchoconstriction comprising administering a compound according to Claim 7 for a time and under conditions effective to treat the bronchospastic and inflammatory component of asthma, coughing, pulmonary irritation, intestinal spasms, spasms of the biliary tract, local spasms of the bladder and of the ureter during cystitis, [and] kidney infections and colics.

9. (twice amended) [A composition according to Claim 7, adapted for use as an] A method of inhibiting bronchoconstriction comprising administering a compound according to Claim 7 for a time and under conditions effective to produce an anxiolytic effect.

14. (amended three times) A method of inhibiting bronchoconstriction comprising administering [for the treatment of the bronchospatic and inflammatory component of asthma, coughing, pulmonary irritation, intestinal spasms, spasms of the biliary tract, local spasms of the bladder and of the uterer during cystitis, and kidney infections and colics, in which] quantities of between 0.02 and 10 mg/kg of body weight of active principle consisting of a compound of formula(I), according to Claim 1, to a patient afflicted with asthma, coughing, pulmonary irritation, intestinal spasms, spasms of the biliary tract, local spasms of the bladder and of the uterer during cystitis, and kidney infections and colics [are administered to the patient] for a time and under conditions effective to antagonize [an] NK-2 receptors.